Effectiveness of intensive practice nurse counselling versus brief general practitioner advice, both combined with varenicline, for smoking cessation

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Effectiveness of intensive practice nurse counselling versus brief general practitioner advice, both combined with varenicline, for smoking cessation: a randomized pragmatic trial in primary care

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ABSTRACT

Aims To study the effectiveness of intensive counselling by a practice nurse (PN) versus brief advice by a general practitioner (GP), each combined with pharmacotherapy, for 6 months' tobacco abstinence (primary outcome). Secondary outcomes included 12-month abstinence, medication adherence and incremental costs per life-year gained. **Design** A multi-site (n = 10), two-group, parallel, pragmatic randomized controlled trial. **Setting** A network of primary healthcare centres in the Netherlands. **Participants** A total of 295 adult daily smokers (mean age = 48 years; mean cigarettes/day = 19). **Intervention and comparator** Patients were randomized to receive individual counselling by a practice nurse (PN) (n = 149) or brief advice by a general practitioner (GP) (146). All patients received 12 weeks of open-label varenicline. **Measurements** The primary outcome was prolonged biochemically validated abstinence from weeks 9 to 26 after treatment initiation. Secondary outcomes included abstinence from weeks 9 to 52, good dosing adherence (> 80% days taken) and incremental costs per life-year gained. **Findings** Abstinence rates in the PN versus GP groups were 32.2% (n = 48) versus 39.0% [n = 57; odds ratio (OR) = 0.71; 95% confidence interval (CI) = 0.44–1.16] from weeks 9 to 26 and 25.5% (n = 38) versus 28.8% (n = 42; OR = 0.84, 95% CI = 0.50–1.43) from weeks 9 to 52, respectively. Values of the Bayes factor indicated that the PN and GP were equally effective. Good dosing adherence was significantly lower in the PN (45.5%, n = 56/123) than in the GP group (62.0%, n = 75/121; OR = 0.45, 95% CI = 0.26–0.77), and the incremental costs per life-year gained were –€416.10. **Conclusions** Among people seeking help to stop smoking from their general practice, one-off brief advice from a general practitioner appears to be as effective as several sessions of behavioural support from a practice nurse when smoking cessation medication is provided.

Keywords Brief advice, counselling, practice nurse, pragmatic trial, primary care, smoking cessation, tobacco, varenicline.

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INTRODUCTION

Tobacco smoking remains a world-wide problem. Primary health care is in a strategic position to assist in smoking cessation support, especially in countries where a large percentage of smokers visit a general practitioner (GP) annually [1,2]. Guidelines recommend that every smoker visiting a GP is advised to quit and is offered treatment—preferably a combination of behavioural support with a pharmacological aid [3–5]. Effective behavioural treatments include brief advice by the GP [6,7] and the pharmacological aids varenicline [8], bupropion [9] and nicotine replacement therapy [10], of which varenicline seems most effective [11–14].

Practice nurses (PNs) are available as an additional work-force in Dutch primary care. They are trained to educate patients, guide medication use and assist to improve their life-styles [15]. However, their added value in smoking cessation treatment has not yet been corroborated by scientific evidence [16]. We hypothesized that PNs are more effective than GPs in helping smokers quit, as they have more time to support patients during their quit attempt [17]. Also, Dutch PNs are trained in giving smoking cessation assistance, so they should have the necessary knowledge and skills to help patients to quit. As a combination treatment is advised by clinical guidelines, it is especially valuable to investigate the PNs' effectiveness when their support is combined with evidence-based pharmacotherapy. We also hypothesized that more intensive support of patients would lead to better adherence to pharmacotherapy. Medication adherence is related strongly to abstinence from smoking [18], and if patients do not receive sufficient support they may be more inclined to stop medication.

The primary aim was to compare the effectiveness of individual counselling by a PN versus brief advice by a GP, both combined with open-label varenicline, on prolonged abstinence from weeks 9 to 26. Secondary aims were to compare: (1) point prevalence abstinence rates at week 9; (2) prolonged abstinence rates from weeks 9 to 52; (3) adherence to varenicline; and (4) short-term cost-effectiveness at week 52.

METHODS

Design

This study was a multi-site two-group parallel randomized controlled trial evaluating intensive counselling from a PN versus usual care from a GP, both combined with open-label varenicline for smoking cessation. A detailed description of the protocol has been published previously [19]. Ethical approval had been obtained (NL30057.068.09/METC 09–03-075), and the study had been registered in the Dutch Trial Register (NTR3067). Recruitment, inclusion and randomization started in October 2011 until December 2013. Treatment and data collection continued until July 2014. During most of the inclusion period, there was no reimbursement for varenicline, while this was free for patients taking part in the trial.

Recruitment

The trial was conducted in a multi-site (n = 10) primary health-care centre in the Netherlands, covering approximately 65 000 patients (www.sge.nl). This large network was used to generate results with high external validity. Patients were recruited by practice assistants, GPs and PNs and via a brief and easily written leaflet displayed in the waiting room. Daily smokers who were 18 years or older, fluent in Dutch, and who had no contraindications for the use of varenicline were included. 'Light' smokers (i.e. smoking fewer than 10 cigarettes per day) were also included: a growing subgroup of smokers in which pharmacotherapy can be effective [2,20]. The GP decided whether or not a patient was eligible for inclusion into the trial and thus if varenicline was prescribed to the individual patient.

Randomization

Eligible smokers were assigned randomly in a 1 : 1 ratio, stratified by health-care centre, using a six-block scheme, by means of a computer-generated random number sequence. The computer disclosed the allocation once during a phone call by a member of the research team with the assistants of the health-care centre, who then contacted the patient to schedule an appointment with the GP or PN. Family members or close friends were paired and randomized in one cluster to protect against contamination across study groups. Blinding of patients and health-care professionals was impossible. The member of the research team who was involved in the randomization procedure was not involved in the primary outcome measurement or data analysis. Data analysists were blinded to group label and identification number.

Sample size

Abstinence rates from weeks 9 to 26 were expected to be 35% in the PN group and 20% in the GP group [19]. The estimated quit rates derived from the results of previous varenicline trials when using varenicline only [11,12] and from one of our own smoking cessation trials that combined individual counselling with nortriptyline [21]. At least 136 patients needed to be included in each group to detect a 15% difference in abstinence with 80% power.

Treatments

PN group

Patients treated by the PN were offered three face-to-face and seven telephone sessions (maximum 120 minutes contact time), starting 1 week prior to the quit attempt until 1 year after the quit attempt, with most contacts scheduled during the first 13 weeks of the quit attempt. There were no consultations with the GP for smoking cessation. PNs had received training in delivering counselling for their routine clinical work according to Dutch guidelines prior to the start of the trial. The counselling protocol was developed through an intensive innovation process involving GPs, PNs and patients [19]. Counselling included the following evidence-based behaviour change

techniques: planning a target quit date; advice on abrupt quitting and the 'not a puff rule'; strengthening motivation and self-efficacy; and enhancing a non-smoker identity [22]. The pragmatic nature of this trial allowed PNs to deviate from the content and planning of the protocol when they believed this would benefit their patient.

GP group

Patients treated by the GP received a minimum of one visit in which the patient received a prescription for varenicline. Dutch guidelines recommend stimulating the patient's motivation during this consultation and to have at least four follow-up visits during several months [3]. However, in daily routine practice only minimal advice is usually given, no quit date is agreed and no follow-up visits are scheduled. Patients were free to contact their GP in case of questions or side-effects.

Varenicline (both groups)

All patients received a prescription of 12 weeks' open-label varenicline during an initial visit with the PN or GP. The usual dosage was recommended, but health-care professionals were allowed to change the dosage when they believed this would be more appropriate for their patient [19]. The starting dose of varenicline was dispensed in the original packaging, and subsequent medication was offered in Medication Event Monitoring System (MEMS®) vials from week 3 until the end of treatment.

Measurements

Primary

The primary outcome measure was prolonged abstinence from weeks 9 to 26 after treatment initiation. Prolonged abstinence was defined as self-reported prolonged abstinence with a maximum of five cigarettes after a grace period of 9 weeks, confirmed biochemically by exhaled carbon monoxide [CO $<$ 10 parts per million], as defined in the Russell Standard [23]. The smoking status was measured and validated biochemically at weeks 9, 26 and 52 after treatment initiation. Randomized patients who withdrew, were lost to follow-up or failed to provide a CO validation were classified as smokers. We also measured the point prevalence rate at week 9 and the prolonged abstinence rate from weeks 9 to 52 after treatment initiation.

Secondary

Information from the Electronic Medical System was used to analyse how many consultations and how much contact time were spent on smoking cessation during a 6-month period after treatment initiation. Information was based on independent codings, which indicated how many minutes the consultation lasted, and on consultations which were registered as encounters for 'tobacco abuse'. A 6-month observation period was chosen because data would have been too contaminated with subsequent quit attempts during longer periods of observation.

Medication adherence was measured with the use of MEMS® vials. Daily adherence (the number of days on which any dose of medication was taken, with a maximum drug holiday of 7 days) and persistence (the duration of medication intake in days with a maximum drug holiday of 72 hours) was calculated for each patient. Daily adherence was then dichotomized into good ($>$ 80% of the prescribed days) or poor adherence. If patients stopped pharmacological treatment within 2 weeks and did not use a MEMS® vial, their medication adherence was zero days for the remaining 10 weeks and was therefore identified as collected.

Background characteristics

Questionnaires were sent at baseline and at weeks 9, 12, 26 and 52 (see Fig. 1). Information from each respondent was collected on: baseline demographic characteristics, self-reported health, past and current smoking behaviour, nicotine dependence, treatment preferences (i.e. PN treatment or GP treatment for smoking cessation), cigarette withdrawal symptoms, smoking-related cognitions, mental health, quality of life, life events, satisfaction with the treatment and possible side effects of varenicline (week 12 follow-up). Also, adverse events reported spontaneously by the patients during telephone or personal follow-up contacts were reported. Members of the research team were not involved in the treatment of patients, and in case of side effects, patients were advised to contact their GP or PN.

Statistical analyses

Statistical analyses were conducted using SPSS and R, with $\alpha = 0.05$ (two-sided) and by calculating 95% confidence intervals (CI). All randomized patients were included in an intention-to-treat analysis [24]. A multiple logistic regression model with a categorical variable for health-care centre and a dummy variable for the treatment group was used to examine whether the odds of prolonged abstinence from weeks 9 to 26 differed significantly between the two groups. To examine the results for treatment effect heterogeneity, a random effect corresponding to the treatment group dummy variable was added to the model. The corresponding variance component was tested with a likelihood ratio test.

We repeated this analysis adjusted for several covariates, chosen a priori, measured at baseline: age, gender, education, income, nicotine dependence, urge to smoke, self-efficacy, duration of longest quit attempt, depression, anxiety, share of smokers in the social

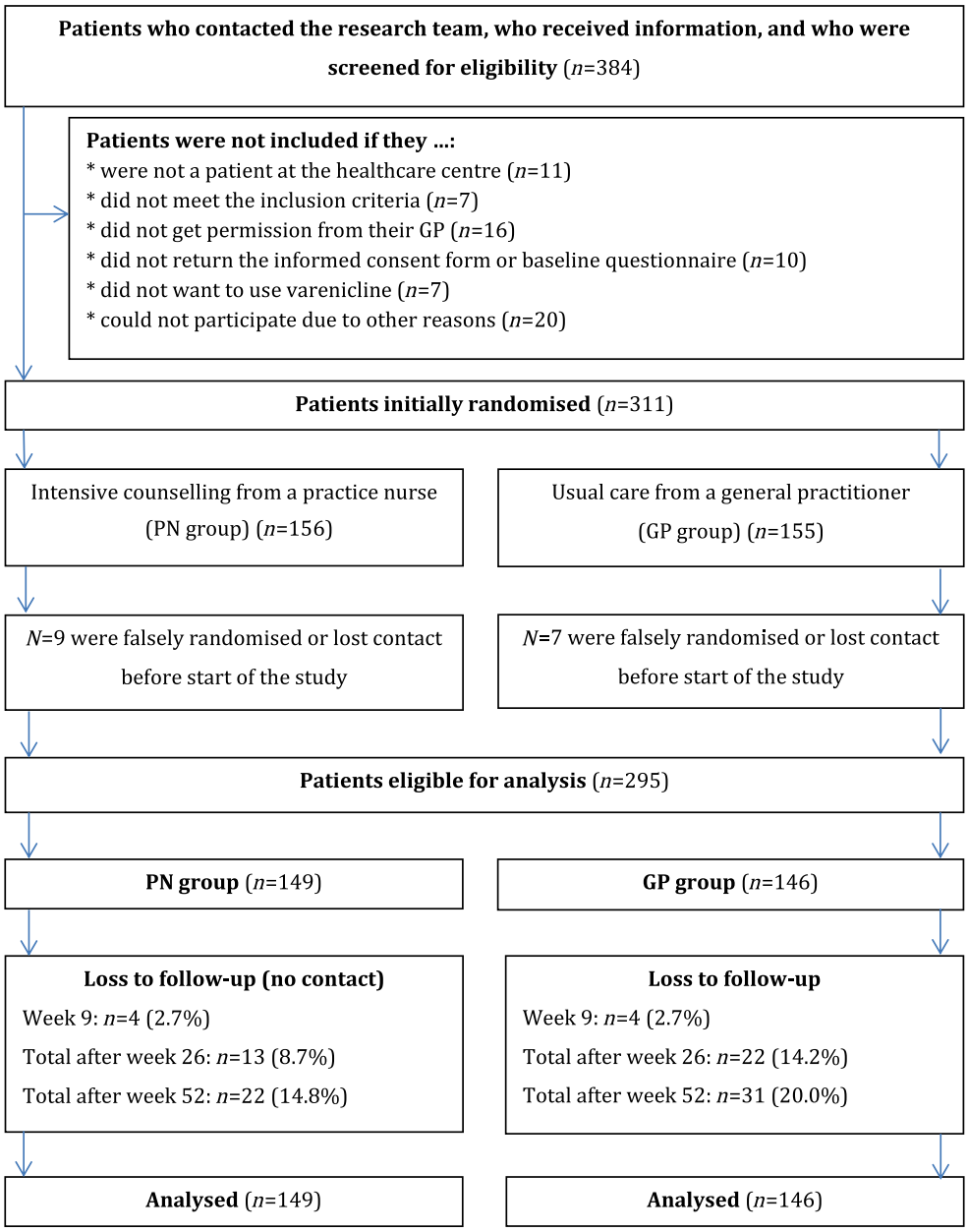

Figure 1 Study flow-chart. [Colour figure can be viewed at wileyonlinelibrary.com]

environment and alcohol misuse [we refer to this as the 'adjusted' odds ratio (OR)] [25–27].

The same analyses were performed to examine the difference in abstinence at week 9 and weeks 9 to 52.

In a *post-hoc* analysis, we calculated Bayes factor to determine the strength of support for the alternative hypothesis (patients treated by a PN are more likely to quit smoking) relative to the null hypothesis (no difference) [28,29]. This is especially useful when faced with non-significant results, as Bayes factor can then be used to determine whether there is simply lack of evidence for the alternative hypothesis or whether the evidence actually supports the null hypothesis. A Bayes factor higher than 1 indicates support for the alternative hypothesis, while a Bayes factor lower than 1 indicates support for the null hypothesis. Values of Bayes factors higher than 3 or lower than 1/3 are regarded as substantial evidence for the alternative or the null hypothesis, respectively.

Daily medication adherence and medication persistence were compared across treatment groups. Median and interquartile ranges were computed because the data showed an expected non-normal (skewed) distribution. Good adherence was analysed using a logistic regression model and was adjusted for the same covariates as the primary analysis. Missing values may not have been missing at random or completely at random, because

patients who were more successful in quitting and/or had more contact with the PN were probably more likely to hand in their MEMS® vial. Therefore, besides a complete case analysis, we also conducted best/worst-case sensitivity analyses for daily adherence, where all missing values in the PN group were replaced by good adherence and all missing values in the GP group were replaced by poor adherence (best case) and vice versa (worst case) [30].

Due to the pragmatic design, a full cost-effectiveness analysis from a societal perspective was not possible. Instead, we calculated the incremental costs per life-year gained. The costs refer to PN and GP consultations during 6 months after treatment initiation derived from the Electronic Medical System and based on independent codings combined with reference prices for Dutch economic health-care evaluations (€17 per PN consultation, €33 per GP consultation) [31]. Cost for varenicline was based on adherence data and the consumer price in 2012 (i.e. €50 per 2 weeks). The life-years gained were estimated based on a method by Stapleton *et al.* [32]. We assumed the 3.5% discounted number of life-years gained that could be attributed to our smoking cessation intervention to be 1.9956 per patient (for the age group 45–54, i.e. the mean age of our sample). The incremental cost-effectiveness ratio (ICER) was calculated as (costs PN group − costs GP group)/(life-years gained PN group − life-years gained GP group).

RESULTS

From 311 smokers who were randomized initially, 16 were found to be ineligible after randomization and were therefore excluded, resulting in a sample size of 295 (range = 9–52 smokers per study site; Fig. 1). Mean age was 48 [standard deviation (SD) = 13.2] years, 22.4% (n = 66) had a low socio-economic status, mean cigarettes per day was 19 (SD = 8.1) and 18.0% (n = 53) were light smokers (< 10 cigarettes per day). The PN (n = 149) and GP (n = 146) group were comparable at baseline, although there seemed to be slightly more men and more patients with cardiovascular disease in the former group (Table 1). Individual confirmation of the patients' smoking status during follow-up was complete in 91% (n = 269) of patients at week 26 and 85% (n = 251) at week 52. There were no differences in attrition rates between both treatment groups at any time-point.

Abstinence

Prolonged abstinence rates in the PN and GP group were 32.2% (n = 48) and 39.0% (n = 57) from weeks 9 to 26 and 25.5% (n = 38) and 28.8% (n = 42) from weeks 9 to 52, respectively (Table 2, Fig. 2). The OR of abstinence from smoking from weeks 9 to 26 in the PN group compared with the GP group was 0.71 (95% CI = 0.44–1.16), and the adjusted OR was 0.76 (95% CI = 0.45–1.30). There was no indication of treatment effect heterogeneity in the

Table 1 Baseline characteristics of patients in the practice nurse (PN) and general practitioner (GP) group.

	PN group (n = 149)	*GP group (n = 146)*
Age, years	47.3 ± 13.4	48.7 ± 12.9
Men	79 (53.0)	60 (41.1)
Education (scale 1–7 = highest)	3.4 ± 1.6	3.6 ± 1.5
Income (scale 1–6 = highest)	3.1 ± 1.3	3.1 ± 1.3
Socio-economic status[a]		
Low	36 (24.4)	30 (20.5)
Medium	95 (63.8)	95 (65.1)
High	18 (12.1)	21 (14.4)
Cigarettes per day	19.3 ± 8.2	18.7 ± 8.0
Nicotine dependence (scale 0–6 = highest level)[b]	3.2 ± 1.3	3.0 ± 1.4
Urge to smoke: how many times (scale 0–5)[e]	2.7 ± 1.1	2.6 ± 1.2
Urge to smoke: strength of urges (scale 0–5)[e]	2.8 ± 0.9	2.7 ± 0.9
Self-efficacy (scale 1–5 = highest level)	2.4 ± 0.8	2.5 ± 0.9
Longest duration of previous quit attempt in years	0.7 ± 1.8	1.0 ± 3.3
Depression (scale 0–21 = highest level)[c]	4.3 ± 3.7	4.0 ± 3.5
Anxiety (scale 0–21 = highest level)[c]	6.8 ± 3.8	6.5 ± 3.5
Share of smokers in social environment (scale 0–5 = highest)[d]	2.3 ± 1.1	2.2 ± 1.0
Alcohol use (scale 0–7 = highest frequency)	3.1 ± 1.9	2.9 ± 2.2
Self-reported current or previous cardiovascular disease	28 (18.8)	20 (13.7)
Self-reported current or previous severe psychiatric condition	3 (2.0)	3 (2.1)

Data are presented as mean ± standard deviation (SD) or n (%). [a]Socio-economic status was based on education and income; [b]measured with the Heaviness of Smoking Index [42]; [c]measured with the Hospital Anxiety and Depression Scale [44]; [d]composite of questions about smokers in social environment: smoking partner (counted double), smoking family members, smoking friends and smoking co-workers; [e]measured with the Strength of Urges To Smoke scale [43].

Table 2 Biochemically validated point prevalence and prolonged abstinence rates in the practice nurse (PN) and general practitioner (GP) group with associated odds ratios and Bayes factors.

Weeks	*Overall (n = 295)*	*PN group (n = 149)*	*GP group (n = 146)*	*OR (95%CI), Bayes factor*	*Adjusted OR (95%CI), Bayes factor*
9	180 (61.0)	86 (57.7)	94 (64.4)	0.73 (0.45–1.19),0.13[a]	0.80 (0.47–1.36), 0.16[a]
9–26 (primary outcome)	105 (35.6)	48 (32.2)	57 (39.0)	0.71 (0.44–1.16), 0.14[b]	0.76 (0.45–1.30), 0.18[b]
9–52	80 (27.1)	38 (25.5)	42 (28.8)	0.84 (0.50–1.43), 0.24[c]	0.98 (0.56–1.72), 0.37[c]

Data are presented as *n* (%) or odds ratio (OR) with 95% confidence interval (CI). The OR was adjusted for health-care centre. The adjusted OR was in addition adjusted for age, gender, education, income, nicotine dependence, urge to smoke, self-efficacy, longest duration of previous quit attempt, depression, anxiety, share of smokers in the social environment and alcohol use. For the computation of the Bayes factors, the effect sizes used to specify the standard deviation for the half-normal distributions representing the alternative hypotheses (see [29] for details) were based on the following hypotheses: abstinence rates in GP and PN group are: [a]52.0 and 29.7% (OR = 2.56) in week 9, [b]35.0 and 20.0% (OR = 2.15) in weeks 9–26, [c]26.5 and 15.2% (OR = 2.00) in weeks 9–52, respectively, based on 136 participants in each group according to the sample size calculation [19]. The estimated quit rates for weeks 9–26 derived from the results of previous varenicline trials when using varenicline only [11,12] and from one of our own smoking cessation trials combining individual counselling with nortriptyline [21]. The estimations for week 9 and weeks 9–52 were extrapolated from that, based on the average percentage point decrease per time-point.

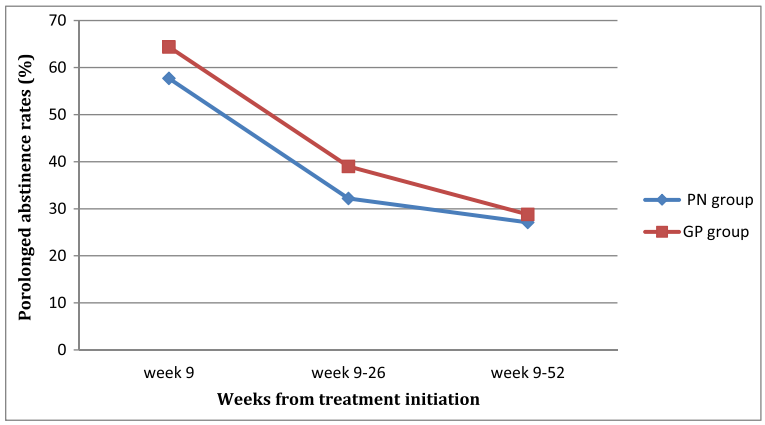

Figure 2 Carbon monoxide-validated prolonged abstinence rates from smoking rates up to 52 weeks after treatment initiation in the practice nurse (PN) and general practitioner (GP) group. [Colour figure can be viewed at wileyonlinelibrary.com]

unadjusted (χ^2 = 0.15, d.f. = 1, P = 0.69) and adjusted (χ^2 = 0.00, d.f. = 1, P = 1.00) models. The OR and adjusted OR of abstinence from weeks 9 to 52 were 0.84 (95% CI = 0.50–1.43) and 0.98 (95% CI = 0.56–1.72), respectively. Again, no statistically significant evidence of treatment effect heterogeneity was found (χ^2 = 1.44, d.f. = 1, P = 0.23 and χ^2 = 1.74, d.f. = 1, P = 0.19 in the unadjusted and adjust model, respectively). Values of the Bayes factor were below or close to 1/3 which supports the null hypothesis, indicating that the PN and GP were equally effective. We noticed considerable variation in the 6-month abstinence rates across health-care centres, ranging from 0 to 63.2%, although the number of included patients was somewhat small in some centres and the corresponding abstinence rates were therefore not reliable (Table 3).

We repeated our primary analysis with a cut-off point of 8 p.p.m. for exhaled carbon monoxide to validate abstinence biochemically [33], which showed exactly the same result. We also repeated our primary analysis in the subgroup of light smokers and found abstinence rates from weeks 9 to 26 of 47.8% (n = 11) in the PN group and 36.7% (n = 11) in the GP group, respectively.

Counselling

The received dose of counselling and the association with abstinence is shown in Table 4. The median number of consultations with the PN was 7 [interquartile range (IQR) = 4–9], and the median time spent was 110 minutes (IQR = 75–135). In the GP group, the median number of consultations was 1 (IQR = 1–2), and the median time spent was 10 minutes (IQR = 10–10). In 41 patients (two from PN, 39 from the GP group), no consultation data were registered. Also, 13 patients in the GP group received counselling from the PN and 13 patients in the PN group had contact with the GP in the context of smoking cessation. A sensitivity analysis in which 59 patients with missing data or who were treated by the wrong health-care provider were excluded did not change the primary outcome.

Treatment preference and satisfaction

Before study enrolment, 67.5% (n = 199) of the patients had a preference for intensive counselling with the PN instead of brief advice from the GP. Additionally, varenicline was expected the most important form of therapy (67.5%,

Table 3 Differences in 6-month prolonged quit rates and self-reported ratings of satisfaction with treatment between health-care centres.

Health-care centre	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Total*
PN group											
Patients (*n*)	13	6	19	9	11	24	20	14	6	16	138
Abstinence[a]	3 (23.1)	0 (0.0)	12 (63.2)	5 (55.6)	5 (54.5)	7 (29.2)	8 (40.0)	2 (14.3)	2 (33.3)	3 (18.8)	48 (34.8)
Satisfaction[b]	7.2 ± 2.44	6.5 ± 2.73	8.5 ± 2.17	9.0 ± 1.12	9.3 ± 0.91	8.3 ± 1.44	7.0 ± 2.09	8.5 ± 2.21	4.0 ± 3.10	8.4 ± 1.31	7.9 ± 2.19
GP group											
Patients (*n*)	11	7	15	8	9	27	25	16	3	15	136
Abstinence[a]	5 (45.5)	2 (28.6)	5 (33.3)	2 (25.0)	4 (44.4)	12 (44.4)	9 (36.0)	10 (62.5)	1 (33.3)	7 (46.7)	57 (41.9)
Satisfaction[b]	6.4 ± 3.35	5.6 ± 3.51	8.4 ± 1.60	7.1 ± 2.03	6.2 ± 3.31	6.2 ± 3.10	5.8 ± 2.89	6.6 ± 2.16	5.0 ± 4.00	5.9 ± 3.43	6.4 ± 2.91

Data are presented as mean ± standard deviation (SD) or *n* (%). [a]biochemically validated prolonged abstinence from weeks 9 to 26 are reported. [b]Satisfaction with treatment was asked in a questionnaire in week 9 and ranged from 1 (lowest level of satisfaction with treatment from the health-care professional for smoking cessation) to 10 (highest). PN = practice nurse; GP = general practitioner. The total number of patients per group deviates from the randomized patients per group, as only the patients who filled in the questionnaire at week 9 were taken into account.

Table 4 Counselling intensity and associated abstinence rates in the practice nurse (PN) and general practitioner (GP) group.

		Patients	*Non-smokers*
PN group (*n* = 149)	*n* sessions with PN		
	1–4	39 (26.2)	4 (10.3)
	5–8	73 (49.0)	26 (35.6)
	>8	37 (24.8)	18 (48.6)
	n minutes with PN		
	15–60	30 (20.1)	4 (13.3)
	61–120	67 (45.0)	18 (26.9)
	>120	52 (34.9)	26 (50.0)
GP group (*n* = 146)	*n* sessions with GP		
	1	117 (80.1)	47 (40.2)
	2	20 (13.7)	7 (35.0)
	>2	9 (6.2)	3 (33.3)
	n minutes with GP		
	10	114 (78.1)	45 (39.5)
	11–20	16 (11.0)	7 (43.8)
	>20	16 (11.0)	5 (31.3)

Data are presented as *n* (%). The presented abstinence rates show prolonged self-reported validated abstinence rates from weeks 9 to 26. The number and time of consultations were extracted from the Electronic Medical Record. No consultations were registered in 39 patients from the GP group and in two patients from the PN group. These data were imputed with 30 minutes and one consultation in the PN, and 10 minutes and one consultation in the GP, as these first consultations were mandatory to receive the medication prescription.

n = 172), compared to intensive counselling by a PN (22.7%, *n* = 58) and brief advice by a GP (9.8%, *n* = 25). Later, at week 9 after treatment initiation, patients were more satisfied with the counselling from the PN (mean = 7.91, SD = 2.19) than with the brief advice from the GP (mean = 6.38, SD = 2.91; $P < 0.001$). As with the quit rates, there were relevant differences between the health-care centres in satisfaction with the received treatment (Table 3).

Daily medication adherence and medication persistence

All patients collected a starting dose of varenicline. In total, we collected medication adherence data in 244 patients (82.7%): 123 and 121 patients in the PN and GP groups, respectively. In the PN group, 45.5% (*n* = 56) had good adherence compared to 62.0% (*n* = 75) in the GP group (OR = 0.45, 95% CI = 0.26–0.77; adjusted OR = 0.37, 95% CI = 0.20–0.67). The best/worst-case sensitivity analyses yielded ORs of 1.12 (95% CI = 0.70–1.81) and 0.24 (95% CI = 0.14–0.39), respectively, neither of which indicated significantly higher chances for good adherence in the PN group (the adjusted ORs led to the same conclusion) (Table 5). Median daily adherence (numeric variable) was 43 days (IQR = 14–73) for the PN group and 69 days (IQR = 17.5–71) for the GP group. Median persistence (time variable) was 38 days (IQR = 10–73) for the PN group and 68 days (IQR = 17–

Table 5 Complete case and sensitivity analyses for adherence.

	Patients analysed	*Good adherence PN group*	*Good adherence GP group*	*OR (95% CI)*	*Adjusted OR (95% CI)*
Complete case analysis	244 (82.7)	56 (45.5)	75 (62.0)	0.45 (0.26–0.77)	0.37 (0.20–0.67)
Sensitivity analysis 1 (best case)	295 (100.0)	82 (55.0)	75 (51.4)	1.12 (0.70–1.81)	1.10 (0.67–1.81)
Sensitivity analysis 2 (worst case)	295 (100.0)	56 (37.6)	100 (68.5)	0.24 (0.14–0.39)	0.20 (0.11–0.35)

Data are presented as *n* (%) or odds ratio (OR) with 95% confidence interval (CI). The OR was adjusted for health-care centre. The adjusted OR was in addition adjusted for age, gender, education, income, nicotine dependence, urge to smoke, self-efficacy, longest duration of previous quit attempt, depression, anxiety, share of smokers in the social environment and alcohol use. Sensitivity analysis 1 replaced all missings for the general practitioner (GP) groups with 'poor adherence' and all missings for the practice nurse (PN) group with 'good adherence'. Sensitivity analysis 2 replaced all missings for the GP groups with 'good adherence' and all missings for the PN group with 'poor adherence'.

71) for the GP group. In both groups a substantial number of patients took medication for longer than the prescribed period, probably by taking only one pill instead of two pills per day: 41 patients in the PN group and 40 patients in the GP group.

Reported side effects

In total, five adverse events were reported, all relating to psychological disorders. One patient died of cardiovascular disease during the trial period. However, this patient belonged to the group which was excluded after randomization, because the GP did not give permission to participate (the patient did not receive any varenicline). An overview of reported side effects in the 12-week questionnaire can be found in Supporting information, Appendix 1.

Incremental costs per life-year gained

Only patients for whom medication adherence data were available were taken into account. Data were available for 123 patients in the PN group and 121 patients in the GP group. This resulted in relatively higher quit percentages for the cost analysis at weeks 9–52: 26.0% (n = 32) and 33.1% (n = 40) for the PN group and the GP group, respectively. The ICER was –€416.10, meaning that the PN group produced fewer life-years gained at higher costs compared with the GP group (Table 6).

DISCUSSION

Intensive smoking cessation counselling by the PN did not increase abstinence rates compared with brief advice from the GP in patients who were treated with open-label varenicline. Overall rates of prolonged abstinence were high at 26 weeks (35.6%) and 52 weeks (27.1%) follow-up. In the GP group, adherence to varenicline was significantly better, and the intervention resulted in more life-years gained at lower costs. Despite the lack of added effectiveness, 70% of the patients had a preference for the PN prior to randomization, and patients treated by the PN were more satisfied with their treatment.

This study revealed high percentages of prolonged abstinence during follow-up in both treatment groups at 26 weeks (32.2%, 39.0%) and at 52 weeks (25.5%, 28.8%) for the PN and GP, respectively. It is also one of the first studies showing quit rates for varenicline with only very limited behavioural support (as in the GP group) in the same range as varenicline studies with much more behavioural support [11,12,34,35]. For example, the study by Swan *et al.* also used varenicline in real life, and showed similar cessation rates when combined with various intensities of assistance (30.7–33.8% at 26 weeks) [34]. In our power calculations, we underestimated the effectiveness of the GP in smoking cessation. A success rate of 35% in the PN group and 20% in the GP group was hypothesized, based on previously published trials [11,12]. We expected a lower quit rate for the GP because of our pragmatic design.

Table 6 Incremental costs (€) and life years (LY) gained in the practice nurse (PN) and general practitioner (GP) group.

	Total (n)	*Costs of varenicline*	*Costs of PN consultations*	*Costs of GP consultations*	*Total costs*	*Abstinence week 9–52 (n, %)*	*Mean LY gained/quitter*	*Total LY gained*	*ICER*[a]
PN	123	25 600	13 515	264	39 379	32 (26.0)	1.9956	616.65	−416.10
GP	121	27 450	204	5082	32 736	40 (33.1)	1.9956	410.10	

The total number of patients differs from the randomized patients as only patients for whom adherence data was available were taken into account. The costs per LY gained were estimated based on a method by Stapleton *et al.* [32]. [a]ICER = incremental cost effectiveness ratio = (total costs PN group – total costs GP group)/(total LY gained PN group – total LY gained GP group).

Although PNs were trained more intensively in giving smoking cessation assistance than the GPs in our study and had much more contact time with the patients, their behavioural counselling did not seem to improve smoking cessation rates. In a randomized controlled trial with a similar design, but from a very different setting (US criminal justice system), behavioural counselling was also not more effective than brief physician advice when combined with pharmacotherapy [36]. Contrary to our hypothesis, medication adherence in the GP group was significantly better than in the PN group, which might partly explain the higher quit rate [18,37]. A possible explanation for the lower adherence in the PN group, as reported previously [36], might be that pharmacotherapy is seen as less important when provided with intensive behavioural counselling than when provided with only very limited behavioural support. It might also be that PNs advised patients earlier to stop the use of varenicline in case of side effects than did the GP.

We found striking differences in effectiveness between health-care centres. Variance between PNs and GPs can occur naturally, despite that the health-care professionals in our study had received the same training regarding smoking cessation. Also, the different social and cultural background of neighbourhoods in which the health-care centres were located could have influenced the results. Patients with a low socio-economic background tend to have more difficulties with succeeding in quitting [38,39]. Selecting a large health-care centre with 10 different locations increased the diversity but also the generalizability of the results.

Although the GP costs per life-year gained were much lower than the PN costs, this result should be treated with some caution. First, the cost-effectiveness analyses used a straightforward and slightly insensitive measure. Secondly, the costs could not be calculated for the total group of patients, as medication adherence data were incomplete. This resulted in a lower relative increase in the smoking cessation rate for the PN than for the GP group (2.0 versus 14.9%), which could have influenced the outcome of cost-effectiveness in favour of the GP. Although it seems likely that treatment by the PN is more expensive, both treatments can be regarded extremely cost-effective [40]. Also, as involving GPs in smoking cessation during routine care is difficult, PNs could still play a crucial role in access and reach of smoking cessation in primary care.

Strengths and limitations

The main strength of the current study is its pragmatic design, which was used specifically to increase the generalizability of our findings. Patients with real-life comorbidities and life-style factors may respond differently to a combination treatment of varenicline with GP advice or PN counselling than selected patients in pre-clinical research settings [41]. A more elaborated overview of the elements that made this study pragmatic can be found in our published study protocol [19]. Although smoking is a bigger problem in patients with a low socio-economic status, smokers with higher socio-economic status are usually more likely to participate in research [39]. In our study, however, patients with low socio-economic status were well represented, which indicates good generalizability of the results. Furthermore, this is the first study assessing and comparing adherence to varenicline in patients treated by GPs and PNs electronically with MEMS®. Also, we succeeded in including a large percentage of potentially eligible patients (76.8% of 384 smokers who contacted the research team).

Nonetheless, some limitations need to be mentioned. The sample size of our trial was large enough to detect the hypothesized difference of 15% in 6-month abstinence rates between the groups, but our statistical power was too low to detect a difference of 10% or lower, which may also be regarded as clinically relevant. Blinding to treatment group was not possible, and some contamination occurred in both groups. The latter could have been prevented by a cluster randomized trial design. However, our practice network did not offer enough clusters, and our sensitivity analysis, excluding patients who crossed over, did not change our primary outcome. We were also not able to monitor the quality of the behavioural support or the treatment fidelity in both groups. This makes it difficult to determine why the intensive consultations by the PN did not lead to more quitters and why there were large differences in effectiveness between health-care centres. Nevertheless, we assume that the PNs in the study are representative for PNs in the Netherlands as a whole. Furthermore, a small number of patients who did not collect varenicline from the pharmacy was excluded. Therefore, results may not be generalizable to every single patient who would enrol in such a cessation programme, but only to those motivated enough to collect medication. As the number of excluded patients was similar in both groups, however, we do not expect this to have biased our results.

CONCLUSION

It is generally possible to achieve high smoking cessation rates in primary care with a treatment programme that combines behavioural support with pharmacotherapy. However, intensive smoking cessation counselling by a PN does not seem to improve abstinence rates compared with brief GP advice in patients who are treated with standardized pharmacotherapy. Nonetheless, both treatments seem extremely cost-effective, and as GPs are difficult to get involved in smoking cessation routinely, PNs can still play an important role in providing

accessible smoking cessation treatment in primary care. The possible mediational effect of adherence should be investigated further, and also why adherence might be better in smokers treated by their GP.

Ethical approval and trial registration

Ethical approval was obtained from the Medical Ethics Committee of Maastricht Academic Hospital and Maastricht University (NL30057.068.09/METC 09–03-075) and the trial was registered in the Dutch Trial Register (NTR3067).

Declaration of interests

D.K. received an unrestricted grant from Pfizer Inc. and The Eindhoven Corporation of Primary Health Care Centers for this investigator-initiated smoking cessation trial. C.S. received funding for research proposals from GlaxoSmithKline and Pfizer. A.L. was a general practitioner at The Eindhoven Corporation of Primary Health Care Centers during the research. All other authors declare that they have no competing interests in relation to this paper.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

Table S1 Reported symptoms and side effects reported in week 12.